


PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference QUETI-SYNR	FOR FURTHER ACTION See Form PCT/PEA/416																									
International application No. PCT/FI2004/000560	International filing date (day/month/year) 23.09.2004	Priority date (day/month/year) 23.09.2003																								
International Patent Classification (IPC) or national classification and IPC C07D281/16, C07D295/18																										
Applicant FERMION OY																										
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>																										
<p>4. This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"><tr><td style="width: 10%;"><input checked="" type="checkbox"/></td><td style="width: 10%;">Box No. I</td><td>Basis of the opinion</td></tr><tr><td><input type="checkbox"/></td><td>Box No. II</td><td>Priority</td></tr><tr><td><input type="checkbox"/></td><td>Box No. III</td><td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td></tr><tr><td><input type="checkbox"/></td><td>Box No. IV</td><td>Lack of unity of invention</td></tr><tr><td><input checked="" type="checkbox"/></td><td>Box No. V</td><td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td></tr><tr><td><input type="checkbox"/></td><td>Box No. VI</td><td>Certain documents cited</td></tr><tr><td><input type="checkbox"/></td><td>Box No. VII</td><td>Certain defects in the international application</td></tr><tr><td><input type="checkbox"/></td><td>Box No. VIII</td><td>Certain observations on the international application</td></tr></table>			<input checked="" type="checkbox"/>	Box No. I	Basis of the opinion	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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Date of submission of the demand 23.06.2005	Date of completion of this report 09.08.2005																									
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Post Address Code



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/FI2004/000560

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	10
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V:

1. The invention relates to a method for the preparation of the dibenzothiazepine compound (I) by ring formation of 2-piperazinoyl-anilino-sulfides of the general formula (II).

The relevant prior art has been cited in the International search report.

D1: US-A-3 539 573 (JEAN SCHMUTZ ET AL) 10 November 1970 (1970-11-10)

D2: DATABASE BEILSTEIN CROSSFIRE BEILSTEIN INSTITUT ZUR
FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, MAIN, DE; Citation
Number 5562436 1988, XP002316545

D3: WARAWA E J ET AL: "Behavioral approach to nondyskinetic dopamine
antagonists: Identification of Seroquel" JOURNAL OF MEDICINAL
CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44,
1 February 2001 (2001-02-01), pages 372-389, XP002213291 ISSN: 0022-2623

D4: WO 02/083624 A (SCHERING CORPORATION; PHARMACOEPIA, INC) 24
October 2002 (2002-10-24)

D5: WO 01/55125 A (EGIS GYOGYSZERGYAR RT; BOZSING, DANIEL;
KOVANYINE LAX, GYOERGYI; SIMIG) 2 August 2001 (2001-08-02)

2. Process claims 1-4

The patent D1 teaches how to obtain dibenzo[b,f]-1,4-thiazepine derivatives bearing a substituted piperazine ring at position 11. In column 6, a synthesis strategy is presented, which proceeds via the intramolecular condensation of amino substituted diphenyl-sulfide-acid amides (XIV), whereby POC13 is suggested as a condensing agent. As an alternative, D1 also teaches the ring closure reaction of diphenyl-sulfide, wherein the amino group is further substituted by an piperazinoyl group (cf. formula XV). It is noted that this alternative has also be disclosed in D5(cf. claim 1). As hydroxyethoxyethyl substituted piperazine derivatives have not been used in cyclisation reactions, novelty is acknowledgeable over the cited prior art.

However, the skilled person, who was looking for a novel route to the present compounds (I), would have considered the teaching of D1 as a convenient manner to achieve the dibenzothiazepine ring closure reaction. As the present compounds do

not bear substituents, which could interfere with the reactive groups involved in the process disclosed in D1 (and D3, D5), the skilled person would have expected that the analogous application to the present starting product (II) will likewise proceed in the desired manner. As D1 clearly sets out the scope of the reaction, wherein inter alia the piperazine moiety may be substituted with further hydroxyalkyl and alkoxyalkyl groups, and the further cited prior art confirms the general applicability, the application of the teaching of D1 to the present starting material is therefore an obvious choice, which does not involve an inventive step in the sense of Art. 33(3) PCT.

3. Intermediate according to claim 10

The present intermediate (III) relates to the hydroxy group protected precursors of the final product (I). Given the presently proposed reaction path, which embraces intermediates having functional groups with comparable reactivity (OH, NH₂), the necessity to protect the terminal hydroxy group by suitable protecting groups is obvious to the skilled person in the art. The compounds used in reaction step h on page 378 of D3, demonstrate that the acyl group is a suitable protecting group employed in analogous dibenzothiazine intermediates with a further substituent at the said benzo part. Hence, the use of acyl protected precursors in the preparation of the final product (I) is not considered to have involved an inventive step in the sense of Art. 33(3) PCT.

4. Intermediates according to claims 5-9

The document D2 (see Reaction ID 3389000 of the cited Database record) teaches how to obtain the genus of the key-intermediate employed in the above discussed synthesis route of D1. In plain analogy to this prior art, which differs merely by the peripheral substituent to the piperazine ring, an ortho-iodobenzoyl-piperazine is coupled to aminothiophenol to give the said key-intermediate. In the light of the teaching of D1, the use of a starting material having the present formula IV is considered to be an obvious choice for the skilled person, who was putting into practice the teaching of D1. By consequence, the subject-matter of claim 5 does not appear to have met the requirements of Art. 33(3) PCT.

As to the subject-matter of claim 6 (unprotected OH) and claims 7-9 (protected OH),

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the requirements of Art. 33(3) PCT have not been met for analogous reasons.